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URINARY TRACT INFECTIONS

Invited Review

Candiduria; a review article with specific data from Iran

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ABSTRACT

Although, several categories of nosocomial infections are presented during the recent years, urinary tract infections (UTIs) considered as one of the most important systemic infections. The presence of *Candida* species in the urinary tract system (Candiduria) is seen in only 10-15% of the cases with UTI, however candiduria has been considered as more problematic infection for patients, laboratory workers and physicians. Due to increasing numbers of several predisposing factors, such as antibacterial agents, urinary tract instrumentation, diabetes mellitus, invasive therapies, and prolonged hospital stay, candiduria develops among the hospitalized patients, especially hospitalized in intensive care units (ICUs) and neonatal intensive care units (NICUs). According to the epidemiological studies, *Candida albicans* is the most common isolated species from candiduric patients. However, during the recent years, due to increasing resistance to antifungal drugs, non-*albicans Candida* species including, *C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis* have been also implicated. We found that the mean prevalence of candiduria among Iranian patients was lower (16.5%) than worldwide ratio and also males were more frequently affected than females (M:F, 1.2:1). Similar to other countries, *C. albicans* was most common infectious agent followed by non-*albicans Candida* species including, *C. glabrata, C. tropicalis* and *C. krusei*.

Keywords: Candiduria; *Candida albicans*; *Candida* species; Iran; urinary tract infection.

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Introduction

Urinary tract infections (UTIs) are the most common nosocomial infections among the hospitalized patients and their incidence has considerably increased during the recent decades.[1-4] Several microorganisms are associated with UTIs including, bacteria, viruses, filamentous and yeasts fungi, however 10-15% of them are caused by *Candida* species, common fungal mycoflora.[5] Funguria is a general term for the presence of several species fungi in the urinary system, such as moulds (*Aspergillus*, *Penicillium*, *Cladosporium*, and *Geotrichum* species).[6-11] However, the presence of *Candida* species in urine are considered as candiduria and its severity varies from asymptomatic candiduria to clinical sepsis.[12,13] In addition, candiduria was defined as the presence of *Candida* >10^4 CFU/mL (colony forming unit / mL of urine) together with pyuria (>10 polymorphonuclear leukocytes/mm^3).[14]

On the other hand, some urologists believe that there are no clear criteria or available recommendations for candiduria. So, candiduria may indicate contamination of the urine samples, lower urinary tract colonization with *Candida*, or true invasive infection of the upper and/or lower urinary tract caused by *Candida* species.[15] As a result, there are several responses by physicians considering the finding of organisms in the urine. The incidence rate of candiduria varies in different reports from different areas.[9,12,16,17]

Clinical and research consequences

Urinary tract infections due to fungi are occurring most commonly as a part of systemic mycosis

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in patients with predisposing factors including immunodeficiency, long-term hospital stays in intensive care unit (ICU) and neonatal intensive care units (NICU), long-term antibiotherapy and chemotherapy, indwelling catheters and elderly patients.[9,12,15,18-20] In addition, some researchers have believed that the incidence of candiduria in teaching hospitals increased due to use of broad-spectrum antibiotics.[18] The new invasive therapies are also raised the incidence of candiduria among patients with cancer and neutropenia.[4,21] In some studies, the mortality rate in candiduria was high and antifungal therapy could not make a significant difference in mortality rates (30%).[19,22] Furthermore, the virulence factors of *Candida* species have an important role in mortality rates.[20] During the last 2-3 decades increasing incidence rates in non-*C. albicans* species of *Candida* such as, *Candida glabrata*, *C. tropicalis*, *C. krusei* and *C. parapsilosis* have been observed that caused a major problem among hospitalized patients due to high resistance to antifungal drugs.[23,24]

Considering the above-mentioned facts, the increasing knowledge of clinicians, researchers and laboratory workers about candiduria, causative agents, laboratory identification methods, and antifungal susceptibility, have an important role in the prophylaxes and effective treatments as well as more accurate selection of antifungal agents for candiduric patients.

Search strategy and study selection

The searching terms were candiduria, UTI, funguria, and candiduric patients. All papers published in full text in English and/or Persian have been selected for review and suitable data have been extracted. Published papers were searched via PubMed, Scopus and Google Scholar. The search of the Iranian literatures was performed by using the international resources; Medline database through PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), Google Scholar (http://scholar.google.com), Google (http://www.google.com) and ISC (http://www.isc.gov.ir/). Moreover, local databases such as, Magiran (http://www.magiran.com) and SID (http://www.sid.ir) have been also searched.

Predisposing factors related to host

Although, *Candida* species, especially *C. albicans* are part of human normal mycoflora, candiduria is rarely present in healthy individuals. On the contrary, it is mostly found in hospitalized patients (ICU and NICU patients) and patients with predisposing factors.[9,25] The impairment of host defense mechanisms (cellular and humoral defenses), damage in anatomical human barriers (burns, invasive surgeries, skin maceration), and underlying diseases can cause an imbalance in the host defence mechanism.[21,23] As a result, the tissues of the hosts are invaded by normal commensal organisms. Patients in both ICU and NICU have often several predisposing factors, such as, diabetes mellitus, immunosuppressive therapy, prolonged antibiotherapy, advanced age, previous surgery (urological and non-urological), leukemia, chronic renal failure, renal transplantation, malignancy, neutropenia, genitourinary tuberculosis and bone marrow transplantation.[9,15,19,20,26-29] Usually, up to 20% of hospitalized patients (especially ICU, NICU patients) may expose to candiduria throughout their hospitalization due to invasive therapeutic and diagnostic procedures.[14,23] Corticosteroid therapy, and patients with hematologic malignancies may also contribute to the development of candiduria among patients.[14,30,31]

Female sex, nephrolithiasis, urinary tract obstruction, the presence of stones and benign prostatic hyperplasia are other predisposing factors for candiduria.[1,27,32] In addition, urinary tract instrumentation such as insertions of Foley catheters, double-J stenting, suprapubic catheters, nephrostomy tubes and hemodialysis were also noted as the predisposing factors for candiduria.[15-17,33] The role of duration of catheterization and antibiotic therapy in the increasing incidence of candiduria has been well discussed in the literature.[1,15,34] Catheters are biomaterials that cause biofilm formation and serve as a portal of entry for *Candida* into the urinary system. Some reports show that 78% of the patients carrying urinary devices have candiduria.[15] On the other hand, the dramatic increase in the prevalence of candidiasis was also observed among patients with acquired immunodeficiency syndrome (AIDS).[35,36] Also, such patients have a high risk of morbidity and mortality.[36]

In Paul et al.[20] study, the class of cephalosporins was the most commonly prescribed antimicrobial agents for patients in whom candiduria was detected. Other researchers believed that there was a strong correlation between candiduria and uncontrolled intake of broad-spectrum antibiotics[24], for example, use of antimicrobial agents as meropenem and ceftazidime.[18] Generally, Guler et al.[21] believed that incidence rates of candiduria increase due to urinary catheterization (12-fold), antibiotic use and urinary tract abnormalities (6-fold), abdominal surgeries (4-fold), diabetes mellitus (2-fold), corticosteroid and immune suppressive administration (1.4-fold).

Pathogenicity of *Candida*

Candida species, especially *C. albicans* are harmless commensal yeasts, and a lifelong resident of human body that cause several superficial, cutaneous, and systemic infections under suitable circumstances. Although the predisposing factors of host have an important role in the development of candidiasis, many pathogenicity factors are associated with microorganism for invading host tissues. Several factors are associated with the pathogenicity of *Candida* including; biofilm formation, extracellular enzymes, germ tube formation and phenotype switching phenomena.[20,37-44] Several studies have shown that the secretion of hydrolytic enzymes, such as proteases, phospholipases, and lipases have an important role in the pathogenesis of *Candida* species.[43,45] Adherence to the tissue surfaces, heat shock

proteins, galvanotropism, and thigmotropism have also been demonstrated and may contribute to the subsequent UTI.[41,46] In addition, some of these factors such as biofilm formation can interfere with antifungal therapy.[5,44] On the other hand, routine antifungal prophylaxis may increase the pathogenicity of *Candida* and resistance to antifungal drugs.[47,48]

Microbiology of candiduria

A broad variety of fungi are associated with fungal UTIs including, filamentous fungi (*Aspergillus* and *Penicillium* species), *Cryptococcus* and *Candida* species.[2,6,7,9,16,49] Various ecosystems such as soils, foods and water are the main sources of *Candida* species. In addition, several species of *Candida* (especially, *C. albicans*) are the mycobiota of gastrointestinal tract, vaginal mucosa, urethra and lungs in humans and animals. They are also as transit saprophytes and colonizing skin and nail of human body. Several reports have shown that nearly 10-15% of nosocomial UTIs are usually caused by *Candida* species[5] and out of more than 200 species of the genus *Candida*, only 12 species are associated with different types of candidiasis.[2,15,35,48]

Candiduria is most commonly caused by *C. albicans* that are detected in 50-70% of urinary isolates, followed by *C. glabrata* (20%) and *C. tropicalis*.[9,17,24,27,29,50] However, incidence rates of other non-*albicans Candida* species; such as *C. parapsilosis*, *C. lusitaniae*, *C. guilliermondii* and *C. krusei* have also increased during last decades.[16,22,37,51] In a study conducted by Paul et al.[20], in India *C. tropicalis* with an incidence rate of 30.5% was the most common microorganism isolated from candiduric patients followed by *C. albicans*. Although, coinfection with bacteria is more common among patients, polymicrobial infections with several yeast species were reported in 5-10% of *Candida*-related UTIs. Interestingly, in most cases, *C. glabrata* appears to be a frequent pathogen in combination with other species.[9,12,16] In addition *Trichosporun* and *Geotrichum* species are rarely isolated from urine samples.[8,9,52]

Epidemiology, sex and age distribution of candiduria

Naturally, due to anatomical and functional characteristics of the urinary tract system, the incidence of candiduria is higher among females than males.[1,21,27] In addition, some of the researchers have believed that this high incidence of candiduria among women may reflect vaginal candidiasis.[15,27] The incidence of candiduria was reported as 57.8% among women by Artiaga Kobayashi et al.[27] in Brazil, 61.9% by Hassaneen et al.[24] in Egypt and 76% by Dalen et al.[34] in Ottawa, Canada. Reports have shown that candiduria develops in different age groups ranging from three months to 81 years.[4,53-55] Several studies have shown that there is a significant association between female gender and candiduria among the HIV-infected patients and ICU patients.[31,36] In addition, in a report from Egypt Hassaneen et al.[24] found that candiduria was more prevalent among female gender, with a female/male ratio of 1.62. On the other hand, Paul et al.[20] indicated that the male:female ratio among candiduric patients was 1.08.

The study has shown that the the incidence of nosocomial UTIs due to *Candida* species increased 22-40% during 1992-1997 when compared with the time interval between 1986, and 1989.[2] Several reports from around the world show that the prevalence of candiduria varies between countries (Egypt 14%[24], and Brazil 22%[27]). In a study, 7.5% and 17.1% of diabetic patients had asymptomatic and symptomatic candiduria, respectively with overall prevalence of 8.3% in Ethiopia.[56]

Direct microscopic examination and urine culture

Suprapubic urine sample is the best urine sample to be used for the diagnosis of candiduria; however the second sterile urine samples are usually used. Asymptomatic catheter-associated candiduria is defined as the presence of a microorganism at a minimum concentration of 10^3 CFU/mL in a urine culture, in the absence of signs and symptoms of a UTI.[34] There are no sensitive/specific laboratory diagnostic tests to distinguish infection from colonization in urine samples. According to literature candiduria can be demonstrated in symptomatic or asymptomatic UTIs.

The presence of *Candida* species in both direct microscopic examinations and/or cultures of urine samples couldn't specifically confirm the presence of UTI. In all candiduric conditions, including contamination, colonization of catheter and infection, *Candida* species may be isolated from urine samples. Although, routinely the second urine samples were collected into the sterile urine bottles (for adults) and disposable urine collection bags (for neonates and children), suprapubic specimens are the best urine samples to be used for diagnostic purposes.[15]

Routine mycology laboratory culture media, such as Sabouraud dextrose agar (SDA), potato dextrose agar (PDA), and nutrient agar with or without an antibacterial are usually used for culture. In addition, during the two last decades a relatively new culture medium (CHROMagar Candida) was incorporated in medical mycology laboratories.[9,24] One of the most important advantages of CHROMagar Candida is to detect polymicrobial growth in urine cultures (Figure 1).[9,54] Although, the best temperature for incubation under aerobic conditions is 35-37°C maintained for 24-48 hours, for slow growing species ambient temperature for one week has been reported.

Urine specimens were usually stained with Gram, Giemsa or methylene blue dyes. In addition, wet mount preparation from the urine sediment can be used for direct examination. Presence of ovoid shaped yeast cells, budding cells (3-15 μm) and pseu-

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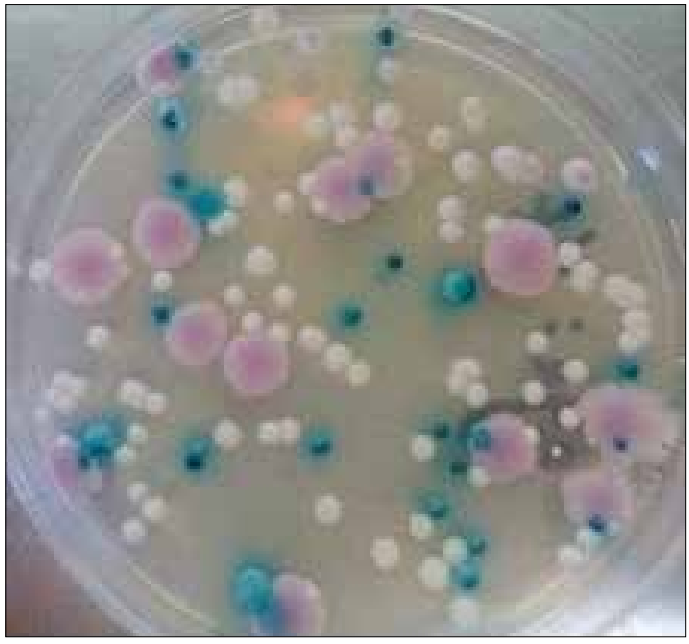

Figure 1. Growth of multi species *Candida* on CHROMagar *Candida* medium

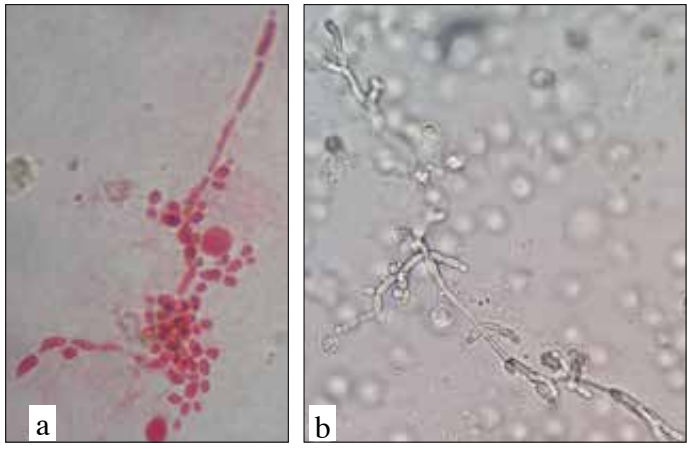

Figure 2. a, b. Yeast cells, budding cells and pseudohyphae of *Candida albicans* in urine sample (a: Fuchsin stained 100×; b: Wet smear)

dohyphae are identifying features of positive direct smears. Candidoma (fungus ball) or granular cyst containing yeast cells, budding cells and pseudohyphae of *Candida* are found in urine samples (Figure 2). The presence of renal fungal balls has been reported in 12% of the cases.[22] Fungal balls are the most frequent manifestation of renal candidiasis in hospitalized neonates in a NICU. Identification of species is usually applied in specific and research laboratories and general laboratories in hospitals can only identify yeast or *C. albicans*. Hence, clinicians always overlook non-*albicans Candida* species that are more resistant to antifungal therapy.

The colony count of *Candida* species in urine samples is an important tool for clinicians in their decision-making process for either finding an effective antifungal for patients or removing urinary catheter. Furthermore, monitoring the treatment process is actually completed by checking the colony count during treatment. Although, candiduria has been defined as the presence of *Candida* species more than 10^4 CFU/mL in urine samples[14], Bukhary believed that clinically significant renal candidiasis might develop even with low colony counts (1000 CFU/mL).[15] Furthermore, the colony counts more than 10^5 CFU/mL, are usually associated with long-term indwelling urethral catheters.[1]

In vitro antifungal assay

Although, antimicrobial-surveillance programmes are providing useful information for empirical therapy, species assignment as well as *in vitro* antifungal assay are usually applied in the specific medical mycology laboratories. As a result, all clinicians have not a specific antifungal susceptibility profile against *Candida* isolates. On the other hand, widespread use of antifungal agents, and increased number of opportunistic fungal infections have increased resistance to available drugs. In the 1990s, azole-resistant isolates of *C. albicans* were found among HIV patients who were receiving long-term antifungal therapy, particularly fluconazole.[57] Literatures have shown that resistance against *Candida* species was first observed against fluconazole and increased progressively during several last decades.[58,59] Furthermore, resistance against other antifungals such as amphotericine B, caspofungin, posaconazole and itraconazole was also reported.[51,60-63]

Out of several antifungal identification tests, microdilution test is the most popular one among medical mycology researchers and CLSI and EUCAST defined specific breakpoints for some clinical important fungi.[25] Recently, modified microdilution technique using Resazurin (colorimetric method) was employed for antifungal susceptibility tests due to rapid measurement of minimum inhibitory concentration (MIC).[25,28,64] E-test and disk diffusion tests are simple and user friendly for laboratory technicians, however these tests were less frequently used by scientists due to their rare availability and lower accuracy. Agar well diffusion is another antifungal assay that is usually used for the evaluation of the *in vitro* antifungal activity with plant extracts.[65] Totally, MIC was measured as MIC ranges, MIC_{50}, MIC_{90} and MIC_{GM} according to above tests for antifungal evaluation *in vitro*. These parameters are relatively associated with clinical outcomes of patients.

Interventions and outcomes

The treatment of candiduria is related to several key factors including presence of a confirmed candiduria using a second, clean-voided urine culture, physical examination, a detailed his-

tory to look for signs or symptoms and the presence of predisposing factors. Although, amphotericin B was traditionally the unique systemic antifungal for UTIs, its toxicity prevented its widespread use for all clinical forms of candiduria and *Candida* species.[66,67] Furthermore, new antifungals such as, fluconazole, flucytosine, voriconazole, itraconazole, posaconazole, isavuconazole and echinocandins (caspofungin) are introduced for therapy during last decades.[50,66-70]

Asymptomatic catheter-associated candiduria is usually a transient and benign condition, and does not associate with invasive candidiasis. In these cases, especially in adult patients hospitalized in ICUs, candiduria presents as fungal colonizations, and antifungal therapy is not required. Disease is resolved spontaneously when catheter is removed. Although asymptomatic candiduria does not need systemic antifungal therapy[18,34], physicians need to confirm the infection by a second sterile urine sample. On the other hand, some authors have believed that 10^3 CFU/mL of *Candida* in urine is sufficient for the diagnosis of infection and immunocompromised patients (diabetes mellitus, leukemia, organ transplants) should be treated with systemic antifungals.[15]

Voltan et al.[23], have believed that UTI due to non-*C. albicans* species such as, *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis* constitute major problems in the hospital environment. Incidence of urinary tract infections due to *C. glabrata* has increased during last decades.[27] Studies have demonstrated that prescribing oral fluconazole for a short-term was effective for the eradication of *Candida* from urine.[27] However, treating candiduria due to non-*albicans Candida* species can be difficult because of resistance to fluconazole.[50] Saha et al.[51], have believed that innate resistance of *C. krusei* to fluconazole may result from hospital practice of empirical administration of the drug which lead to selection of resistant species.

On the other hand some studies have shown that mortality rate of 26.2% was seen among candiduric patients and the most common predisposing factors associated with death are related to urinary tract instrumentation devices, antimicrobial therapy, ICU hospitalization, renal failure, and use of umbilical venous catheter.[20,25] However, candiduria among the critically ill newborn in NICUs can be a sign of a disseminated infection, especially candidemia. Although, spontaneous resolution occurred among patients with asymptomatic candiduria in several studies, treatment with fluconazole eradicated candiduria in 60.8%[27]-50% of the cases.[71]

Generally, fluconazole is the first choice antifungal drug for candiduria, however in resistant cases, flucytosine is a useful alternative.[72] During the last decades, new effective antifungals belonging to echinocandin class were introduced into clinical usage. In a case series study, Lagrotteria et al.[50] found that micafungin may be used for the treatment of candiduria due to less susceptible strains of non-*albicans* species.

Candiduria in Iran

The Islamic Republic of Iran is located in western Asia, north of Persian Gulf and Oman Sea. It is the second-largest country in the Middle East with 1,648,195 km^2 and with over 81 million inhabitants. The first available documented data about candiduria in Iran was reported by Zaini et al.[73], in 1993 and more recently published papers have illustrated candiduria pattern in Iranian hospitals so far. Disease is approximately widespread in Iranian people, however, its frequency vary in different provinces. The mean prevalence of candiduria was approximately 16.5% in Iran, with highest rate (32.3%) in Qazvin and the lowest in Khuzestan (5.2%).[12,53]

Totally in Iran the most common etiologic agents of candiduria were *C. albicans* (58.53%), followed by *C. glabrata* (15.39%), *C. tropicalis* (5%), *C. krusei* (2.72%), *C. parapsilosis* (1.53%), *C. kefyr* (1.03%), *C. lusitaniae* (0.42%) and *Candida* species (14.72%). Furthermore, uncommon yeast / yeast-like microorganisms such as *C. albidus* (0.23%), *C. laurentii* (0.07%), *Geotrichum* (0.12%) and unidentified yeasts (0.22%) were also isolated from urine samples.[9,12,17,25,28,31,33,47,49,53,55,74-77] Furthermore, rarely *Trichosporum* and *Saccharomyces* were isolated from patients' urine cultures.[73] In addition, recently Moslem et al.[77], isolated *Rhodotorula* species from a patient with candiduria in Ahvaz. Furthermore, co-cultures of different species of bacteria (*Staphylococcus* and *Escherichia* species) with *Candida* species were identified in several investigations.[25,78]

Although in some reports, candiduria was more commonly seen among Iranian female population[9,17,53,75], but overall, our review have indicated that candiduria was more prevalent among male population with a male:female ratio of 1.2:1. Furthermore, age range of the candiduric patients varied between 5 days and 81 years, however mostly middle aged patients were affected. [9,12,17,25,28,31,33,47,49,53,55,74-77]

In conclusion, candiduria due to nosocomial UTI is relatively more common among patients with specific predisposing factors. Host factors (genitourinary abnormality, diabetes mellitus, and immunodeficiency) as well as invasive therapy (indwelling urinary catheters, widespread systemic antibiotic use, surgery, and chemotherapy) have important roles in the prevalence and increasing rate of candiduria in patients. Moreover, pathogenicity factors of organisms and specific species, non-*albicans Candida* species (resistance to antifungals), are other factors that change the incidence of disease, antifungal susceptibility and mortality rates. We found that the mean prevalence of candiduria among Iranian patients was lower (16.5%) than

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worldwide prevalence rate and also males were more frequently affected than females (M:F, 1.2:1). Similar to other countries, *C. albicans* was the most common agent followed by non-*albicans* species including, *C. glabrata*, *C. tropicalis* and *C. krusei*.

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